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The Role of *Aeromonas* in Diarrhea: a Review

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Abstract
The evidence for an enteropathogenic role of *Aeromonas* spp. is still controversial. This review examines various parameters related to a causative role of *Aeromonas* and concludes that infraspecific subsets of strains with a particular array of enterotoxin genes are potential enteropathogens. The consequences for stool bacteriology are discussed.

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Introduction

The genus *Aeromonas* [1] consists of facultatively anaerobic Gram-negative rods that are predominantly motile by a single polar flagellum and produce oxidase, catalase, nitrate reductase, and an array of exoenzymes. Most species are mesophilic. Members occur in water sources, soil, and foodstuffs. They can be agents of disease in poikilothermic animals (e.g., fish, reptiles) and in man.

The following infections in man have become known [2]:
(a) wound infections or cellulites related to water or soil exposure;
(b) septicemia, mainly associated with malignancies (particularly hematological) or hepatobiliary disease, rarely with diabetes mellitus or no immune defect;
(c) localized extraintestinal infections such as meningitis, peritonitis, otitis media, endocarditis, osteomyelitis, etc.

The first case of a human *Aeromonas* infection reported was one of myositis, observed in 1954 in a woman from Jamaica [3]; and the first series of infections was published from the author's laboratory in 1968 [4]. Since 1961, when the first strain was isolated from human feces [5], aeromonads have been incriminated as agents of diarrhea but the evidence for enteropathogenicity has never been unequivocal [6] because various yardsticks used to solve the question have proven insufficient, including Koch's original postulates and their expansion into a "unified concept" by *Evans* [7]. For the clinician, the clinical microbiology laboratory, and public health authorities, however, a solution would be of considerable importance: a positive answer would mean to search for aeromonads in practically every stool specimen by means of selective media (which are different from those used for other bacterial enteropathogens) [8], and to decide whether to treat patients with fecal aeromonads and whether to regularly check drinking water for the presence of these organisms. In fact, the US Environmental Protection Agency has already included *A. hydrophila* in the Contaminant Candidate List of organisms which require future regulation under the Safe Drinking Water Act [9].

The purpose of this review is to examine and interpret the data that have accumulated over approximately 40 years and to make some, albeit preliminary, recommendations for the clinical laboratory. Right now, most laboratories have their own rules regarding the isolation of aeromonads from stools. *Aeromonas*-associated diarrhea (A.-a.d.) will be defined as loose stools associated with the isolation of aeromonads in the stool.

Diarrhoic Patients vs Controls

Of the 17 phenospecies of the genus *Aeromonas* [1, 2], only four have been isolated from human feces with significant frequencies: *A. hydrophila*, *A. caviae*, *A. veronii* biovar. *sobria* (formerly "*A. sobria*"), and *A. trota*; i.e., hybridization groups (HG) 1,4,8, and 14. The latter is a "newcomer" whose frequency was probably underestimated in earlier studies since it is susceptible to ampicillin, an agent used in many selective media for aeromonads [8]. *A. jandaei* (HG 9) and *A. schubertii* (HG 12) have been rare fecal isolates [10]. If these species are agents of diarrhea, one should expect that they are more frequently present in patients with A.-a.d. than in controls [7]. Appropriate studies would have used such controls, selective media, speciation of the

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isolates, and would have eliminated samples containing aeromonads together with other enteropathogens.

While not all studies have included enteropathogenic *Escherichia coli*, viruses, and parasites, results of those available have been contradictory. Not only did the ranking of aeromonads differ from first [11–13] to fifth [14] among enteropathogenic bacteria, but there were also differences in seasonal distribution and predominating species. Some studies observed isolation peaks in warmer seasons [12, 13, 15], others saw no seasonal preference [16]. *A. caviae* was the predominating species in most studies, followed by *A. hydrophila* and *A. veronii* biovar. *sobria* [6, 12, 13, 16, 17]. *A. hydrophila* predominated in Brazil [18] and Thailand [19]; in Bangladesh, it was initially *A. caviae* [20] but later *A. trota* [21] (it should be kept in mind that later studies used more advanced methods of identification and differentiation). In Finnish residents traveling in Morocco, *A. veronii* biovar. *sobria* came in first [22]. While some studies did find significant differences in the frequency of aeromonads isolated from diarrhoic patients including travelers [22] as opposed to controls [12, 14–16], others did not [17, 23, 24]. One study found differences in children – more prone to diarrhea anyway – but not in adults [25]. In Thailand, the difference was significant for Peace Corps volunteers but not for indigenous people [19]. The average isolation rate from diarrhoic stools was 0.8 to 7.4%; in healthy controls, it was 0.4 to 2.1% [26]. Individual studies, however, vary widely in this regard, e.g., a study of infants in Peru found 52.4% in diarrhoic patients vs 8.7% in controls [12]. Of note, if the concomitant enteropathogens were removed from the statistics and isolates were speciated, the significant difference between patients and controls would disappear in this study. The frequency of copathogens was also high in India and Bangladesh (ci. 40%; 10,14) and in Chile (50%, 23). Control groups showed frequencies of 0 to 2.1% in Western Europe and the USA [15, 17, 25] and higher ones in warmer climates (4.8% in Bangladesh, 5.2% in Chile) [14, 23]; in Peru, they ranged from 0 to 21.4% [12]. The carrier state was transient [16], sometimes involving multiple phenotypes [10, 13, 27]. Ranking of individual species was generally equal in patients and controls [12, 17]. Finally, a quantitative study showed considerable variations in the number of colony-forming units (CFU) of aeromonads during different sampling periods, and CFU overlapped between patients (3.5 to 9.9 log10 CFU/gm stool) and controls (5.7 to 6.0 log10 CFU/gm) [11]. In another study, the amount of growth on a selective (Monsur agar) plate was not associated with the presentation of diarrhea [6].

Symptomatology

Symptoms of A.-a.d. were quite variable. Stool consistency varied from loose to watery to bloody; and diarrhea was either self-limited , lasting up to one week, or took a prolonged course of up to two weeks, or became "chronic" with more than one month duration [11, 13, 15]. Nausea, abdominal cramps, fever, and vomiting were observed only in part of the patients [11, 13]. In one study, duration was longer and fever more prominent with *A. caviae* than with *A. hydrophila* or *A. veronii* biovar *sobria* [13]. While in the majority of patients the small intestine seemed to be affected only, up to one-third showed colitis by endoscopy [11, 28, 29]. A few cases of hemolytic-uremic syndrome (HUS) following A.-a.d. [2, 30, 31] but no cases of reactive arthritis have been reported.

Similar to some cases of bacterial gastroenteritis, low stomach acidity, liver and gastrointestinal disease as well as recent therapy with antimicrobials ineffective against aeromonads have been reported as associated factors [11, 13, 32]. AIDS patients, however, did not show a higher frequency of A.-a.d. than non-AIDS patients [33].

Cessation of diarrhea following therapy with antimicrobials effective against aeromonads has been reported [11] but its significance for a causation of diarrhea remains questionable in view of the frequently self-limited course of A.-a.d. More significant would be the disappearance of diarrhea or of colonic lesions together with newly negative stool cultures, as has been reported for single cases [11, 28, 29, 34]. This could, of course, also be due to a self-limited disease or to a transient state of colonization with aeromonad(s) [16, 27] in the presence of other enteropathogens. Unfortunately, follow-up typing of carrier isolates has never been done.

Common-Source Outbreaks and Transmission of Fecal Isolates

Although outbreaks are well known for enteropathogenic bacteria, the evidence for outbreaks with aeromonads is almost non-existent in spite of their ubiquitous occurrence in water sources like drinking water [9] and in foods such as seafood, meat, and vegetables [35].

The first outbreaks of A.-a.d. were reported from two day care centers where 6 of 25 and 5 of 24 diarrhoic children, respectively, yielded fecal *Aeromonas* strains [36]. However, the PFGE patterns differed in all except two strains. Of 17 diarrhoic patients from Wisconsin whose stools contained aeromonads, 14 had their drinking water examined for these organisms; only one source was positive. Additional isolates from private wells were unrelated by PFGE to patient isolates [9]. A similar result was obtained in another study using ribotyping [37]. Conversely, during a 68-week observation period in Melbourne in which 795 stool samples from diarrhoic patients were examined, none yielded aeromonads but half of the drinking water samples of the patients, drawn weekly, yielded the organisms [38]. In another study from Wisconsin, A.-a.d. was more often associated with consumption of aeromonad-free drinking water than with consumption of untreated water [39]. Seemingly in contradiction was a study associating A.-a.d. with drinking untreated water but that water had not been examined for aeromonads [32].

Two tropical outbreaks have been reported. In one [40], 28 of 69 patients admitted during one month to a Benghazi, Libya, hospital had "*A. sobria*" isolated from their stools. A source could not be found. The biochemical characteristics suggested *A. hydrophila* but the identification was questionable because the strains produced hydrogen sulfide. In the other report [41], six children in a hematology-oncology unit in Chandigarh, India, developed acute A.-a.d. with "*A.sobria*" during a four-week period. All isolates had similar biotypes and antibiograms. Since neither study had used controls or molecular typing they cannot be used as proof for the presence of an outbreak.

That molecular methods are crucial in this connection was also shown in cases where transmission might have occurred from food, the environment or from patient(s) to patient(s). In one suggestive case of transmission from egg salad, no typing had been done [42]. In a further study mentioned previously [31], several isolates of "*A. sobria*" were cultured from an aquarium with which an infant had contact. The infant developed A.-a.d. and HUS . While all *A. sobria* isolates produced aerolysin (see below) and the diarrhea disappeared with the disappearance of *A. sobria* from the stool, the isolates from the aquarium and from the stool were not identical in their nucleotide sequences (in view of the multiplicity of environmental types it may, however, have been possible that not enough colonies had been checked). In this connection, it is of interest that studies on *Aeromonas* strains from patients` environments have revealed that identical ribotypes may be found in epidemiologically related, but also in unrelated strains [43]. In one instance, *A. caviae* was isolated from three children, from their mother, and from well water used by them. Ribotyping showed identical types in the children but unique patterns in the mother and in the well water [44]. Cultures of *Aeromonas* strains in India obtained during a two-year period have shown multiple types, virulence genes, and antibiograms [10].

Only two studies have found identical ribotypes to suggest transmission, one from food (shrimp) to a patient with A.-a.d. [45] , and another one from a child to her foster parents [44]. The outbreak of food poisoning with diarrhea after consumption of Swedish "landgang", however, from which 6 to 7 log10 CFU/gm of enterotoxin-producing *A. hydrophila* was isolated, lacked stool cultures to prove the causative agent [46].

Experimental Infections

Surprising for an allegedly enteropathogenic organism, oral challenge of 57 human volunteers with 5 different *A. hydrophila* strains producing cytotoxin and cholera toxin-reactive factor (presumably Act) as well as "hemolysin" (see below), using 4 to 10 log10 CFU, led only to mild/moderate diarrhea in two participants who received 7 and 9 log10 CFU, respectively. 55 remained unaffected, although most became colonized [47]. Likewise, oral challenge of protein-malnourished mice [48] or of mice pretreated with streptomycin [49] or clindamycin [50] led to colonization only. In the highly artificial RITARD (removable intestinal tie adult rabbit diarrhea) model [51] using 12 isolates of three *Aeromonas* species from A.-a.d. patients and from carriers diarrhea, bacteremia, and death were strain-dependent. Diarrhea was seen in 23 of 37 rabbits who died and in 11 of 27 who survived ($p = 0.15$). Bacteremia was found in 36 of the moribund ones and in 2 of the survivors. Colonization was detected in all animals but, as in studies mentioned previously [16, 27], lasted only up to 10 days. The ileum was the most heavily colonized part of the intestine.

Host Response

Similar to other diarrheas in which the causative agent is found in the intestine only, serum assays for antibody responses in A.-a.d. have shown insufficient sensitivity and specificity. 7 of 10 sera from patients with A.-a.d. showed no agglutinating antibodies; 5 of these 7 had titers of 1:16 to 1:64 by passive hemagglutination, but that was similar to controls [32]. An ELISA for IgM and IgG responses to the lipopolysaccharides (LPS) of homologous strains had a sensitivity of 30% and a specificity (vs healthy blood donors) of 74% [52]. A cytotoxin-neutralizing assay had a 46% sensitivity and a 94% specificity; only patients with severe acute diarrhea over 60 years of age reacted positively [52]. In a case of HUS following A.-a.d., these neutralizing antibodies showed rising titers [30]. SIgA responses to fecal extracts of 13 patients with A.-a.d. showed fourfold or more titer increases in 11 by dot-blot and in 8 by Western blot but were limited to *A. hydrophila* and "*A. sobria*"; two patients with *A. caviae* did not react [53]. If extracellular products similar to hemolytic toxins were used, specific sIgA responses were seen in 11 of 13 extracts from patients with A.-a.d [54]. Neither study had examined carriers or blood donors.

Virulence Factors: Occurrence

Aeromonads may produce a variety of biologically active extracellular substances similar to virulence factors known in other enteropathogenic bacteria. They include fimbriae, flagella, outer membrane proteins, an S layer, lipolpolysaccharides (endotoxin), capsules, proteases, glycerophospholipid:cholesterol acyl transferase (GCAT), and siderophores (amonabactin, enterobactin) [26, 55]. Their relationship to enteropathogenicity has not been elucidated except that type IV pili have been reported to be associated with gastroenteritis [56].

Toxins of particular interest for gastrointestinal infections, i.e., enterotoxins, are also present in aeromonads [26, 55] and were found to be chromosomally encoded [57]. All cause fluid secretion in rabbit ileal loops. They include:

– the cytotoxic, heat-labile (56 °C, 20 min) type II-secreted enterotoxin Act which is also hemolytic and

destroys the intestinal epithelium via cytokines and activation of the arachidonic acid metabolism;
- two (the heat-labile Alt and the heat-stable Ast) cytotonic enterotoxins which cause an increase in intracellular cAMP and prostaglandins and elongate Chinese hamster overy (CHO) cells;
- various hemolysins, among them AerA , HlyA, Ahh1, Asa1[59, 60], and the "*A. sobria*" hemolysin [61] which increases intracellular cAMP. It should be emphasized that hemolysis on blood agar plates used in the clinical laboratories is not a reliable indicator of hemolysin production since it depends on other factors such as the animal source of the erythrocytes and, in experimental models, the number of passages in ileal loops [51, 62, 63]. Generally, erythrocytes are hemolyzed on sheep blood agar plates by *A. hydrophila* and *A. veronii* biovar. *sobria* but rarely by *A. caviae*.

Here again, studies have found the cytotoxin more frequently in *Aeromonas* isolates from diarrhoic patients than from carriers [64] while in Brazil, the heat-stable cytotonic toxin, the cytotoxin and adhesins were not more frequent in diarrhoic patients than in controls [18]. Others found them more frequently in isolates of *A. hydrophila* than in those of *A. caviae* and *A. veronii* biovar. *sobria* but not more often in diarrhoic than in carrier or environmental strains [23]. The presence of various hemolysins did not show any relationship to the occurrence of diarrhea in one study [6].

Fecal, extraintestinal, and environmental strains of *A. hydrophila*, *A. caviae*, and *A. veronii* biovar. s*obria* were recently found to have a type III secretion system [65].

Virulence Factors: Genetic Analysis

In a study of Bangladeshi children [21], DNA probes were used for identification of the genes for the enterotoxins. *Act* was never found alone, and only in the species *A. hydrophila* together with the other two genes. Diarrhoic children yielded significantly higher numbers of isolates carrying *alt* plus *ast* than carriers and environmental samples but yielded lower numbers of isolates than environmental strains that carried *ast* only. For isolates with *alt* alone and for different *Aeromonas* species, significant differences in the frequency of these genes between the three types of samples could not be detected. The presence of *alt* plus *ast* was associated with watery stools whereas *alt* alone was associated with loose stools. It was concluded that *alt* plus *ast* may synergistically lead to more severe diarrhea, whereas *act* was found associated with bloody diarrhea [21]. In the Indian study [10], only diarrhoic isolates were investigated and yielded a similar distribution as in [21] for *alt* between the species but not for *act* and *ast.* Transposon mutants of an A.-a.d. isolate of *A. hydrophila* which affected the transcription of *act* resulted in reduced virulence by 2 log10 in mice when injected intraperitoneally. Culture filtrates of isogenic mutants with a truncated *act* caused no damage to the microvilli, did not show hemolytic activity any more, and showed reduced mouse virulence by 3 log10. Reintegration of the native *act* resulted in complete restoration of its former activity [67]. Knockout mutants caused by marker-exchange mutagenesis showed reductions in fluid secretions in ileal loops by 64, 48, and 43% in mutants affecting *act*, *alt*, and *ast*, respectively [66].

Double knockout mutants showed reductions of 36, 62, and 73% in *alt* plus *ast*, *act* plus *ast*, and *act* plus *alt*, respectively. A triple knockout mutant failed to elicit fluid secretion. The greatest damage, thus, seemed to come from *act*, followed by *alt* and *ast* [67].

Genes for hemolysis were found in a majority of *A. hydrophila* and *A. veronii* biovar. *sobria*, but not of *A. caviae*, from diarrhoic patients [6, 60]. The absence of *hly* and *aer* has led to a 20-fold reduction in the LD 50 in a suckling mouse model [61]. Deletion of the gene encoding the *Aeromonas* OMP which is a structural component of the type III secretion system resulted in a significant reduction in inflammatory cytokines and chemokines in the sera of infected mice [68].

Conclusions

At this time, it seems as if only certain infraspecific subsets of aeromonads provided with certain genes for enterotoxicity are significantly associated with diarrhea, the best evidence arising from genetic analysis. Falkow's proposed "molecular Koch Postulates" [69] would almost have been fulfilled, depending on the interpretation of the first postulate. Unfortunately, this will be of little help to the clinical microbiologist and to public health personnel. The microbiologist may, however, base his judgment upon the obvious rarity of person-to-person transmission, the lack of proven outbreaks and of experimental pathogenicity for man, and the frequently self-limited character of A.-a.d. At the present time, he may, therefore, decide to limit the search for aeromonads in stools to those from patients with chronic diarrhea for which no other cause can be found. The epidemiologist will, however, insist on isolation and species identification, if not typing. The fact that recovery of aeromonads from water did not correlate with recovery from stool suggests caution in recommending public health measures to control aeromonads in water.

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